REMARKS

Claims 12 - 25 are before the Examiner for consideration.

Rejection under 35 U.S.C. §101

The Examiner has rejected claims 12 – 21 under 35 U.S.C. §101 because the claims are written as "use" claims.

In response to this rejection, Applicant has amended claims 12 – 21 as set forth above so that they are no longer written as "use" claims. In particular, Applicant has amended claims 12 – 19 to recite a method for treating diseases caused by infectious agents, *e.g.*, viruses, bacteria, parasites, and fungi. In addition, Applicant has amended claim 20 to recite a composition for treating diseases caused by infectious agents, *e.g.*, viruses, bacteria, parasites, and fungi. Claim 21 has been amended to depend from claim 20. Applicant submits that as amended, claims 12 – 21 recite proper method and composition claims. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw this rejection.

Rejection under 35 U.S.C. §112, first paragraph

Claims 12 – 21 have been rejected under 35 U.S.C. §112, first paragraph because the specification does not enable the prevention of any and all viral, bacterial, and fungal infections.

In response to this rejection, Applicant has amended claims 12 and 20 as set forth and discussed above respect to the rejection under 35 U.S.C. § 101. In particular, Applicant has amended claims 12 – 19 to recite a method for treating diseases caused by infectious agents, *e.g.*, viruses, bacteria, parasites, and fungi and has amended claim 20 to recite a composition for treating diseases caused by infectious agents, *e.g.*, viruses, bacteria, parasites, and fungi.

Applicant submits that as amended, claims 12 – 21 are directed to the treatment of diseases caused by infectious agents and not to the prevention of any diseases. Thus, Applicant submits that claims 12 – 21 are sufficiently enabled and respectfully requests that the Examiner reconsider and withdraw this rejection.

Rejection under 35 U.S.C. §112, first paragraph

Claims 12 – 21 have been rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one of skill in the art to make and/or use the invention. In particular, the Examiner asserts that Kunzmann *et al.* (*Immunobiology*, Vol. 197, p. 221) teach that bisphosphonates activate γδ T cells, which is the opposite of what is described in the specification. The Examiner has requested an explanation.

Applicant submits that Kunzmann *et al.* disclose that aminobisphosphonates can stimulate a distinct subset of T-cells (*i.e.*, Vγ9Vδ2 T cells) and do not teach the activation of any γδ T cells by any bisphosphonates as the Examiner asserts. Moreover, the specification indicates that in the presence of an infectious agent (*e.g.*, parasites, viruses, microorganisms, etc.), the immune system is manipulated into stimulating immunosuppressive γδ T cells, thereby stimulating a T cell response to suppress a suitable immune response to combat the infectious agent. (*See, e.g.*, paragraph bridging pages 1 – 2 of the specification and Jomaa *et al., FEMS Immunol. Med. Microbiol.* 1999; 25(4); 371-378 cited therein). However, according to the present invention, stimulated immunosuppressive γδ T cells in such a manipulated immune system can be inactivated by bisphosphonates. As a result, a suitable immune response to attack the infectious agent can be initiated. Thus, the effect of the bisphosphonate depends on the condition of the immune system.

In view of the above, Applicant submits that the claims are sufficiently enabled and respectfully requests that the Examiner reconsider and withdraw this rejection.

Rejection under 35 U.S.C. §112, second paragraph

Claims 12, 13, 15, and 18 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. In particular, the Examiner asserts that the use of the phrases "such as" and "in particular" are indefinite.

In response to this rejection, Applicant has amended the claims to remove the phrases "such as" and "in particular" and has added new dependent claims 22 and 23 directed to the subject matter recited in the "such as" and "in particular" phrases. Applicant submits that the claims as amended are sufficiently definite and respectfully requests that this rejection be reconsidered and withdrawn.

Rejection under 35 U.S.C. §112, second paragraph

Claims 12 – 21 have been rejected under 35 U.S.C. §112, second paragraph as being indefinite. The Examiner asserts that the language "use of" and "or compounds which, on administration, form the compounds to be administered as metabolites or breakdown products, for the production of pharmaceutical preparations" is confusing.

In response, Applicant has amended the claims to remove the objected claim language and has amended the claims to recite method and composition claims instead of use claims. In view of the above, Applicant submits that the claims are sufficiently definite and respectfully requests that this rejection be reconsidered and withdrawn.

Rejection under 35 U.S.C. §102(b)

Claims 12, 13, 14, 16, 20, and 21 have been rejected under 35 U.S.C. §102(b) as being anticipated by Gertz *et al.* (U.S. Patent No. 5,270,365). The Examiner asserts that Gertz *et al.* disclose bisphosphonates that are useful for treating periodontal disease caused by bacteria, which assertedly reads on the present claims.

Applicant respectfully traverses this rejection in view of the following remarks.

Applicant submits that Gertz *et al.* do not teach or suggest a method of treating diseases caused by infectious agents, *e.g.,* viruses, bacteria, parasites, and fungi, that includes administering an effective amount of a bisphosphonic acid of formula I (*e.g.*, 4-amino-1-hydroxybutylidine-1,1-bisphosphonic acid) which inactivates γδ T cells or a composition for treating diseases caused by infectious agents that includes a bisphosphonic acid of formula I which inactivates γδ T cells as presently claimed. It is evident from reading column 3, lines 22 – 33 and 44 – 64 of Gertz *et al.* that bisphosphonates do not attack the cited bacteria, which is responsible for periodontal disease. In order for a reference to be anticipatory, each and every claimed element must be found within the four corners of the cited reference. Because Gertz *et al.* do not disclose or otherwise teach the use of bisphosphonates for treating diseases caused by an infectious agent or a composition for treating diseases caused by infectious agents that includes a compound of formula I which inactivates γδ T cells as presently claimed, Gertz *et al.* cannot be an anticipatory reference for the present claims.

In view of the above, Applicant respectfully submits that the present invention is not anticipated by Gertz *et al.* and respectfully requests that the Examiner reconsider and withdraw this rejection.

Rejection under 35 U.S.C. §102(b)

Claim 12 has been rejected under 35 U.S.C. §102(b) as being anticipated by Pauls *et al.* (U.S. Patent No. 5,563,128). The Examiner asserts that Pauls *et al.* teach phosphonate derivatives that are useful in treating fungal infections and that these phosphonate derivatives fall within the scope of the claims.

Applicant respectfully traverses this rejection in view of the following remarks.

Applicant submits that although Pauls *et al.* disclose bisphosphonic acid compounds, Pauls *et al.* do not teach or suggest the compounds claimed in independent claims 12 and 20. When formula I of the present invention is compared to formulas I – V and VII – XIV of Pauls *et al.*, R_2 would correspond to the multiple-substituted long chains appearing to the right of $(CRR)_f$ (see, *e.g.*, columns 5 – 8 of Pauls *et al.*). The chains depicted in these formulas of Pauls *et al.* contain at least two aromates (*e.g.*, Ar I and Ar II; aryl or aralkyl). However, the chain corresponding to R_2 of the compounds claimed in amended independent claims 12 and 20 do not include these long, multiple-substituted chains that contain two aromatic groups. Because Pauls *et al.* do not disclose or otherwise teach the chains corresponding to R_2 as claimed in amended claims 12 and 20, Pauls *et al.* cannot be an anticipatory reference for the present claims. Thus, Applicant respectfully submits that amended independent claims 12 and 20 are patentably distinguishable over Pauls *et al.*, and that all claims dependent therefrom are non-anticipatory, non-obvious, and patentable.

In view of the above, Applicant respectfully submits that the present invention is not anticipated by Pauls *et al.* and respectfully requests that the Examiner reconsider and withdraw this rejection.

Rejection under 35 U.S.C. §102(b)

Claims 12 - 21 have been rejected under 35 U.S.C. §102(b) as being anticipated by Ramamurthy *et al.* (U.S. Patent No. 6,114,316). In particular, the Examiner asserts that Ramamurthy *et al.* teach a combination of bisphosphonate compounds and tetracycline for treating microbial, viral, and fungal proteinase mediated conditions which assertedly reads on the present claims.

Applicant respectfully traverses this rejection in view of the following remarks.

Ramamurthy *et al.* teach a composition and a method for inhibiting tissue destructive conditions and membrane degrading proteinases (*see, e.g.,* column 6, lines 30 – 33). In addition, Ramamurthy *et al.* disclose that the preferred bisphosphonates for use in the disclosed compositions and methods are alendronate, clodronate, elidronate, pamidronate, medronate, nedrinate, tiludronate, and zolendronate (*see, e.g.,* column 8, lines 25 – 29). Further, in Ramamurthy *et al.,* , the target for using the bisphosphonates is a proteinase (*i.e.,* MMP, serinproteinase). (*See, e.g.,* column 3, lines 6 – 17, column 6, line 63 – column 7, line 2, and column 7, lines 46 – 58). However, there is no teaching or suggestion within Ramamurthy *et al.* of treating diseases caused by infectious agents, let alone treating the diseases with a bisphoshhonate compound as claimed in claim 12. Nor is there any teaching or suggestion of a composition for treating diseases caused by infectious agents that includes the bisphosphonate compound of formula 20. Thus, Ramamurthy *et al.* do not teach or suggest a method of treating diseases caused by infectious agents, *e.g.*, viruses, bacteria, parasites, and fungi, that includes administering an effective amount of a compound of formula I, *e.g.*, 4-amino-1-hydroxybutylidine-1,1-bisphosphonic acid, which inactivates γδ T cells or a composition that treats diseases caused by infectious agents and includes a compound of formula 1 which inactivates γδ T cells as presently claimed. As discussed above, to be an anticipatory reference, each and every claimed element of the claimed

invention must be found within the four corners of the cited reference. Because Ramamurthy *et al.* do not disclose or otherwise teach the use of bisphosphonates for treating diseases caused by an infectious agent or a composition for treating diseases caused by infectious agents that includes a compound of formula I which inactivates γδ T cells as presently claimed, Ramamurthy *et al.* cannot be an anticipatory reference for the present claims.

In view of the above, Applicant respectfully submits that the present invention is not anticipated by Ramamurthy *et al.* and respectfully requests that this rejection be reconsidered and withdrawn.

Rejection under 35 U.S.C. §103(a)

Claims 12 – 21 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Byington *et al.* (*Experimental Parasitology*, 87, 194 – 202 (1997)) in view of Gertz *et al.*, Pauls *et al.*, and Ramamurthy *et al.* The Examiner asserts that Byington *et al.* teach that bisphosphonates such as etidronate, pamidronate, and alendronate can be useful in treating certain parasitic infections. The Examiner concludes that it would have been obvious to one of skill in the art to use known bisphosphonates for treating viral, bacterial, or fungal infections because a sufficient number of bisphosphonates have demonstrated such activity.

Applicant respectfully traverses this rejection in view of the following remarks.

Pyrophosphates play an important role in biochemistry, namely, they are involved in kinase activity. Byington *et al.* teach pyrophosphate analogues, which are not the subject of the claimed invention. Consequently, one of ordinary skill in the art would not have arrived at the claimed bisphosphonates by using the computer based homology method and related binding studies as taught in Byington *et al.* (*see, e.g.*, Abstract). Furthermore, Byington *et al.* do not teach or suggest the inventive concept of using the claimed bisphosphonates to inactivate γδ T cells for the effective treatment of infection.

In addition, as discussed above with reference to Gertz *et al.*, Pauls *et al.* ,and Ramamurthy *et al.*, none of these references teach or suggest administering an effective amount of a compound of formula I to inactivate γδ T cells to treat diseases caused by an infectious agent or teach a composition for treating diseases caused by an infectious agent that includes a compound according to formula I as presently claimed. Moreover, Pauls *et al.* do not even disclose the compounds claimed in amended claims 12 and 20. Because none of Gertz *et al.*, Pauls *et al.*, and Ramamurthy *et al.* teach or suggest the method claimed in amended claim 12 or the composition claimed in amended claim 20 and because Gertz *et al.*, Pauls *et al.*, and Ramamurthy *et al.* do not make up for the deficiencies of Byington *et al.*, the combination of Byington *et al.* in combination with Gertz *et al.* and/or Pauls *et al.* and/or Ramamurthy *et al.* would result in the presently claimed invention.

Moreover, Applicant submits that there is no motivation for one of skill in the art to arrive at the presently claimed invention based on the disclosures of the cited references. Motivation to combine references must come from the teachings of the prior art, the nature of the problem being solved by the references being combined, or the knowledge of one of ordinary skill in the art. There is simply no motivation from any of these sources to administer compounds of formula I to inactivate γδ T cells and treat viral, bacterial, or fungal infections of a compound including a compound of formula I to inactivate γδ T cells. as presently claimed. Accordingly, Applicant respectfully submits that amended independent claims 12 and 20 are patentably distinguishable over Gertz *et al.* and/or Pauls *et al.* and/or Ramamurthy *et al.* As such, claims 12 and 20, and all claims dependent therefrom, are non-obvious and patentable.

In view of the above, Applicant submits that the present invention is not obvious over Byington *et al.* in view of Gertz *et al.* and/or Pauls *et al.* and/or Ramamurthy *et al.* and respectfully request that the Examiner reconsider and withdraw this rejection.

CONCLUSION

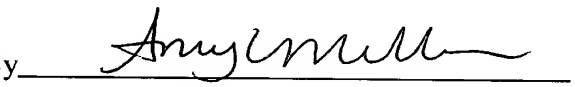
In light of the above, Applicant believes that this application is now in condition for allowance and therefore request favorable consideration.

If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 08-0750 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

HARNESS, DICKEY, & PIERCE, P.L.C.

By 

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